

Gentamicin Pharmacokinetics and Pharmacodynamics during Short-Daily Hemodialysis

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Key Words

Gentamicin · Hemodialysis · Pharmacokinetics · Renal failure

Abstract

Background/Aims: Gentamicin pharmacokinetics have not been described in patients undergoing short-daily hemodialysis (SDHD). The aim of this study is to describe gentamicin pharmacokinetics and dialytic clearance (Cl_{dial}) in SDHD patients and simulate gentamicin exposure after six dosing regimens to help guide future dosing. **Methods:** Six anuric patients undergoing SDHD were enrolled. Patients received intravenous infusion of 2 mg/kg gentamicin on day 1 after the first HD session followed by HD sessions on days 2, 3, and 4. Blood samples for determination of gentamicin concentrations were serially collected. Gentamicin pharmacokinetic parameters and Cl_{dial} and interindividual variability terms (IIV) were estimated using NONMEM VII. Influence of patient weight on systemic clearance (Cl_s) and central volume of distribution (V_c) and influence of urea removal estimates on Cl_{dial} were assessed. The model was used to simulate gentamicin concentrations after six dosing regimens including pre- and postdialysis as well as daily and every-other-day dosing. **Results:** A two-compartment model with first-order

elimination from central compartment described gentamicin pharmacokinetics. Population estimates for Cl_s and Cl_{dial} were 7.6 and 134 ml/min, respectively. Patient weight was statistically significantly associated with Cl_s and V_c . Predialysis every-other-day regimens were as effective ($C_{max} \geq 8$ mg/l and $AUC_{48 h} \geq 140$ mg·h/l) and less toxic ($C_{min} < 2$ mg/l and $AUC_{48 h} < 240$ mg·h/l) than postdialysis regimens. **Conclusions:** Estimated gentamicin Cl_{dial} is higher than previous estimates with thrice-weekly regimens. Predialysis every-other-day dosing may be recommended during SDHD.

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Introduction

Bacterial infections remain the second leading cause of death in patients with chronic kidney disease, stage 5 (CKD-5) [1]. Aminoglycosides remain critical for treating multidrug-resistant Gram-negative and Gram-positive infections [2, 3]. Optimization of aminoglycoside dosing to ensure maximal efficacy and minimal toxicity is essential. The best predictors of efficacy are the ratios of peak aminoglycoside plasma concentration (C_{max}) or area under the curve (AUC) to the minimum inhibitory concentration. Hence, dosing regimens that maximize

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these are expected to maximize efficacy and prevent emergence of resistant strains [4].

Short-daily hemodialysis (SDHD), usually 2 h done 6 days per week, is an effective alternative to conventional thrice-weekly 4-hour hemodialysis. SDHD improves quality of life and reduces medical complications (i.e. blood pressure reduction, hyperkalemia, inflammation) associated with CKD-5 [1, 5, 6].

The purpose of this study was to describe gentamicin pharmacokinetics in patients undergoing SDHD. Furthermore, the estimated gentamicin pharmacokinetic parameters were used to perform simulations to predict gentamicin exposure after six different dosing regimens.

Subjects and Methods

Six noninfected anuric subjects undergoing outpatient SDHD at the Indiana University Outpatient Dialysis Center (Indianapolis, Ind., USA) were enrolled in the study. Subjects were eligible for the study if they were 18 years of age or older, received regular SDHD six times weekly, suffered from no other acute illnesses, and had a postdialysis weight within 30% of ideal body weight [7]. Subjects were excluded from the study if they had a history of gentamicin allergy or if they received gentamicin within 3 weeks of enrollment. The study protocol was approved by the Indiana University-Purdue University-Indianapolis Institutional Review Board. All subjects provided written informed consent before participating in any study procedures. All study procedures were conducted in the Indiana Clinical Research Center as part of the Indiana Clinical and Translational Sciences Institute at Indiana University Hospital (Indianapolis, Ind., USA).

Each subject received a 2-mg/kg gentamicin intravenous infusion over 30 min ($n = 5$) or 60 min ($n = 1$) on day 1 after the first SDHD session. Blood samples were collected at the end of the dialysis session immediately before drug administration and then at 0.5, 1, 1.5, 2, 3, and 5 h after the end of dialysis/start of the gentamicin infusion. On day 2, blood samples were collected just before the start, at the middle (1 h), and at the end of the second SDHD session and then at 0.5, 1, 2, and 4 h after the end of the dialysis session. On days 3 and 4, blood samples were collected before the start, at the middle (1 h), and at the end of the dialysis sessions. All samples were collected in nonheparinized evacuated blood collection tubes and allowed to clot. Samples were centrifuged and serum was harvested and stored at -70°C until analyzed in batch. Dialysis procedures were performed using a new unused cellulose triacetate high-flux dialyzer (Exeltra 150; Baxter Healthcare, Deerfield, Ill., USA). The dialyzer had an ultrafiltration coefficient of 31.5 ml/h per mm Hg and a surface area of 1.5 m^2 . Serum gentamicin concentrations were determined using an enzyme multiplied immunoassay technique (EMIT; Syva Co., Dade Behring Inc., Cupertino, Calif., USA) [8]. The lower limit of quantification for the assay was $0.5\text{ }\mu\text{g/ml}$ with calibration curves constructed for concentrations up to $10\text{ }\mu\text{g/ml}$. Intraday and interday coefficients of variation were less than 12% at $1\text{ }\mu\text{g/ml}$ and $8\text{ }\mu\text{g/ml}$. Urea nitrogen and creatinine concentrations were determined by colorimetric methods [8, 9]. This assay had intra- and

interassay coefficients of variation of $<5\%$ for both urea nitrogen and creatinine.

Gentamicin serum concentrations from all subjects were used simultaneously to perform population compartmental pharmacokinetic modeling using NONMEM (version VII; Globomax LLC, Ellicott, Md., USA). Initially, gentamicin concentrations on day 1 only (after the first SDHD session and before the second session) were used to describe gentamicin disposition without the effect of dialysis. A two-compartment structural pharmacokinetic model [8] was used to describe gentamicin pharmacokinetics during interdialysis periods (equations 1 and 2):

$$\frac{dX(1)}{dt} = R_0 - \frac{Cl_s}{V_c} \cdot X(1) - \frac{Cl_d}{V_c} \cdot X(1) + \frac{Cl_d}{V_p} \cdot X(2) \quad (1)$$

$$\frac{dX(2)}{dt} = \frac{Cl_d}{V_c} \cdot X(1) - \frac{Cl_d}{V_p} \cdot X(2) \quad (2)$$

where $X(1)$ and $X(2)$ are the amounts of drug in the central and peripheral compartments, $dX(1)/dt$ and $dX(2)/dt$ are the rates of change in drug amount over time for central and peripheral compartments; V_c and V_p are the apparent volumes of distribution in the central and peripheral compartments, respectively; R_0 is the zero-order infusion rate; and Cl_s and Cl_d are the systemic and distribution clearances, respectively.

The above model was used to obtain population parameter estimates during interdialysis periods. Subsequently, gentamicin concentrations from days 1–4 were used in the overall model that describes the additional effect of SDHD on gentamicin pharmacokinetics. Effect of dialysis on gentamicin elimination was modeled using a third compartment representing the dialyzer. Gentamicin dialysis clearance (Cl_{dial}) into the third compartment was turned on and off according to the schedule of dialysis sessions. Equation 1 was modified to express Cl_{dial} as shown in equation 3, whereas equation 5 was used to describe change in gentamicin amounts in the dialysis compartment, and equation 4 described change in gentamicin amounts in the peripheral compartment.

$$\frac{dX(1)}{dt} = R_0 - \frac{Cl_s}{V_c} \cdot X(1) - \frac{Cl_d}{V_c} \cdot X(1) + \frac{Cl_d}{V_p} \cdot X(2) - \frac{Cl_{dial}}{V_c} \cdot DIAL \cdot X(1) \quad (3)$$

$$\frac{dX(2)}{dt} = \frac{Cl_d}{V_c} \cdot X(1) - \frac{Cl_d}{V_p} \cdot X(2) \quad (4)$$

$$\frac{dX(3)}{dt} = \frac{Cl_{dial}}{V_c} \cdot DIAL \cdot X(1) \quad (5)$$

An indicator variable 'DIAL' with values of 1 or 0 was used to turn the dialysis compartment on and off, respectively, depending on the timing of daily dialysis sessions [8]. Transfer of drug between the three compartments was assumed to be following first order processes.

Interindividual variability (IIV) on Cl_s , V_c , and Cl_{dial} was modeled using an exponential IIV model assuming log-normal distribution of the between-subject variability in population parameter estimates. Each subject's estimated Cl_s , V_c , and Cl_{dial} were therefore related to the corresponding population estimate. Residual unexplained variability, including intraindividual vari-

Table 1. Dosing regimens used to simulate gentamicin exposure

Regimen	Initial loading dose mg/kg	Follow-up doses mg/kg	Timing of follow-up doses
A ₁	2	1	immediately after every other SDHD
A ₂	2	0.5	immediately after each SDHD
B ₁	3.1	2.75	1 h before every other SDHD
B ₂	3.1	1.375	1 h before each SDHD
C ₁	3	3	1 h before every other SDHD
C ₂	3	1.5	1 h before each SDHD

ability, was modeled using an additive error term. The best structural model to describe the observed data was chosen based on goodness-of-fit plots and minimum value of objective function (OFV), as well as individual plots of observed and model-predicted concentrations versus time.

The final structural model was used to test the effects of subject and dialysis covariates on the model parameters. The effects of subject weight on population parameter and IIV estimates for Cl_s and V_c were examined. Similarly, to determine if there was a significant impact of urea removal on gentamicin removal, the effects of single-pool Kt/V_{urea} , equilibrated Kt/V_{urea} , and weekly standard Kt/V (as dialyzer-specific covariates) on Cl_{dial} were evaluated. All urea removal estimates were calculated using standard methods previously described by Leyboldt et al. [9]. Covariates were kept in the model if their addition resulted in a statistically significant decrease in OFV (a decrease of 3.84 units is considered statistically significant at $\alpha = 0.05$ using a χ^2 test). The relationship between subject weight and each of Cl_s and V_c was described using a power model after correcting each subject's weight for the median weight value according to equation 6:

$$P_{TV} = \theta_1 \cdot \left(\frac{WT}{91} \right)^{\theta_2} \quad (6)$$

where θ_1 is the typical value (population estimate) of the parameter (Cl_s or V_c) in a subject weighing 91 kg (median weight for the 6 subjects), WT is the subject weight, and θ_2 is the power term describing the effect of subject weight on typical value of the parameter. A similar approach was used to test the effects of dialyzer-specific covariates on Cl_{dial} , but with no correction of subject values to the median of the population.

The final model (including covariates) was used to simulate gentamicin plasma concentrations using NONMEM VII after six different dosing regimens, A₁, A₂, B₁, B₂, C₁, and C₂, as shown in table 1 in order to determine the best dosing strategy in patients undergoing SDHD. All doses were simulated as 30-min infusions, and plasma concentrations were simulated for a 1-week interval. Two of those regimens (B₁ and C₁) had been tested in a previous study [10]. Previous studies have proposed the use of $AUC \geq 140$ mg·h/l/48 h and $C_{max} \geq 8$ mg/l as pharmacodynamic targets indicating achievement of concentrations high enough to cause bacterial killing [8, 11]. Similarly, $AUC \leq 240$ mg·h/l/48 h and $C_{min} < 2$ mg/l were proposed as targets indicating achievement of concentrations low enough between doses to avoid toxicity (i.e. non-

toxic). We used these same targets to evaluate the performance of six different dosing regimens.

Areas under the simulated plasma concentration versus time curves (AUC) were calculated using the linear trapezoidal method for the time intervals 0–48 (AUC_{0-48}), 48–96 (AUC_{48-96}), and 96–144 (AUC_{96-144}) based on the simulations. Percentages of simulated subjects achieving a 48-hour interval $AUC \geq 140$ mg·h/l/48 h, a 48-hour interval $AUC \leq 240$ mg·h/l/48 h, a peak plasma concentration ≥ 8 mg/l (30 min after the end of infusion), and a trough (predialysis for regimen A and predose for regimens B and C) plasma concentration < 2 mg/l were calculated.

Results

Six subjects (1 woman and 5 men) enrolled in and completed the study. Subjects had a median age of 54 years (28–59) and a median weight of 91 kg (59–110). No adverse effects related to gentamicin were reported. The dialysis blood flow rate in all subjects was 500 ml/min. The median (range) dialysis duration was 2.5 h (2.0–2.5). Observed gentamicin plasma concentration-time profiles were described by a two-compartment model with first order elimination from the central compartment. The effect of dialysis was described by a third compartment with Cl_{dial} controlling the one-way transfer of drug from the central to the dialysis compartment during intradialysis periods. Table 2 shows the model-estimated population pharmacokinetic parameters with the associated IIV where applicable. Addition of IIV terms on only Cl_s , V_c , and Cl_{dial} led to significant improvement in the model evident by a significant decrease in the OFV.

The structural pharmacokinetic model was used to examine the effects of different subject and dialysis covariates on the estimated pharmacokinetic model parameters and the associated IIV parameters. Subject weight was significantly associated with Cl_s and V_c as evident from the drop in OFV of 15 and 5 points upon addition of subject weight as a covariate on Cl_s and V_c , respectively. The addition of subject weight as a covariate on Cl_s led to a marked decrease in IIV estimate from 55.7 to 0.3%. Similarly, addition of subject weight as a covariate on V_c led to a decrease in IIV from 90.7 to 50.7%. The relationship between subject weight and each of Cl_s and V_c was explained by equations 7 and 8, respectively:

$$Cl_{s,TV} = (7.6) \left(\frac{WT}{91} \right)^{1.97} \quad (7)$$

$$V_{c,TV} = (12.1) \left(\frac{WT}{91} \right)^{2.27} \quad (8)$$

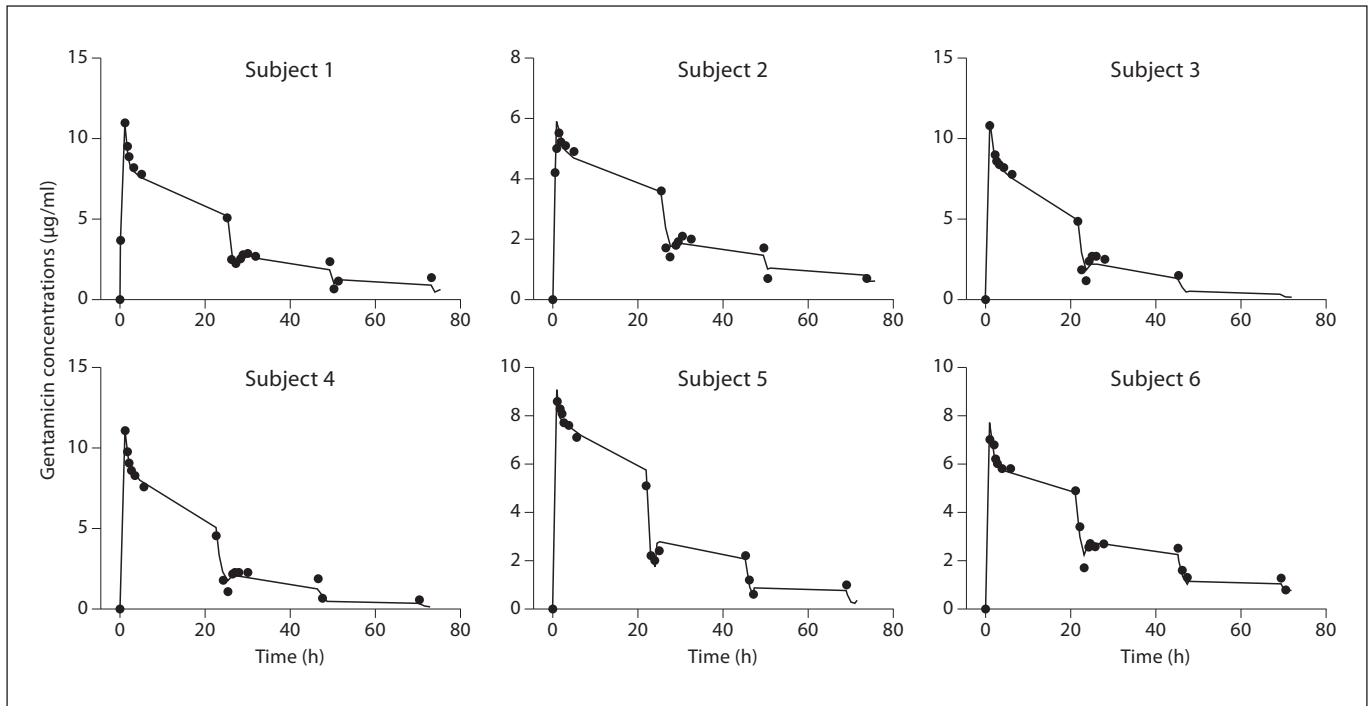


Fig. 1. Observed and model-predicted gentamicin plasma concentration-time profiles for the 6 subjects. Solid lines represent the model individual predicted concentrations and the closed circles represent the observed concentrations.

Table 2. Gentamicin population pharmacokinetic parameter estimates for the structural and the covariate models

Parameter	Structural model			Final covariate model		
	population estimate	relative standard error %	IIV	population estimate	relative standard error %	IIV
Cl_s , ml/min	6	20.8	55.7	7.6	5.5	0.3
V_c , liters	9.5	38.1	90.7	12.1	23.2	50.7
V_p , liters	10.6	2.2	NA	10.5	5.1	NA
Cl_d , ml/min	116.2	12.3	NA	128.7	8.8	NA
Cl_{dial} , ml/min	139.5	15.2	34.5	134.2	15.9	29.3

NA = No interindividual variability was estimated for that parameter.

where $Cl_{s,TV}$ and $V_{c,TV}$ are the population estimates of systemic clearance and apparent volume of distribution in central compartment and WT is the subject's weight. The power terms describing the effects of subject weight on the Cl_s and V_c were estimated to be 1.97 with a relative standard error of 24.8% and 2.27 with a relative standard error of 54.6%, respectively. Table 2 shows the final pa-

rameter estimates from the final covariate model. The final covariate model was able to accurately predict the observed gentamicin plasma concentration-time profiles for the 6 subjects as shown in figure 1. There was no statistically significant impact of single-pool Kt/V_{urea} , equilibrated Kt/V_{urea} , and weekly standard Kt/V (as dialyzer-specific covariates) on Cl_{dial} (data not shown).

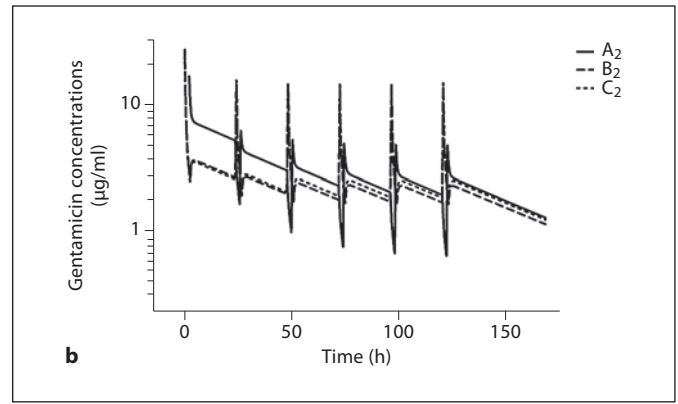
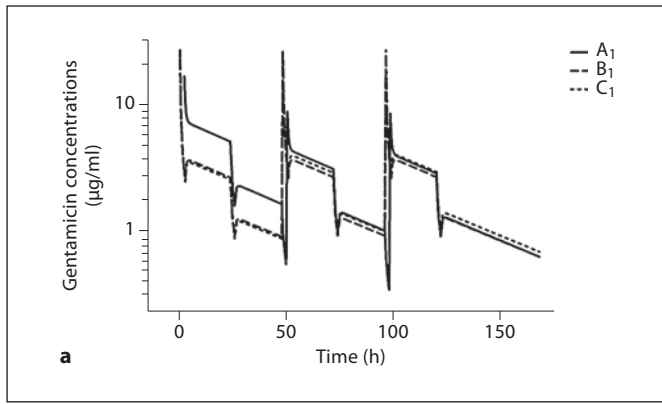


Fig. 2. Simulated concentration-time profiles (mean of 1,000 simulations) for every-other-day (a) and daily (b) regimens. Regimen A₁ = Initial dose of 2 mg/kg followed by follow-up doses of 1 mg/kg after every other SDHD session; Regimen A₂ = initial dose of 2 mg/kg followed by follow-up doses of 0.5 mg/kg after each SDHD session; Regimen B₁ = initial dose of 3.1 mg/kg followed by

follow-up doses of 2.75 mg/kg after every other SDHD session; Regimen B₂ = initial dose of 3.1 mg/kg followed by follow-up doses of 1.375 mg/kg after each SDHD session; Regimen C₁ = initial dose of 3 mg/kg followed by follow-up doses of 3 mg/kg after every other SDHD session; Regimen C₂ = initial dose of 3 mg/kg followed by follow-up doses of 1.5 mg/kg after each SDHD session.

Table 3. AUC, peak, and trough gentamicin plasma concentrations on days 1, 3, and 5 following each of the six simulated dosing regimens

Regimen	Day 1			Day 3			Day 5		
	AUC, mg·h/l	C _{max} , mg/l	C _{min} , mg/l	AUC, mg·h/l	C _{max} , mg/l	C _{min} , mg/l	AUC, mg·h/l	C _{max} , mg/l	C _{min} , mg/l
A ₁	208 ± 29	10.7 ± 2.1	1.9 ± 0.3	132 ± 16	6.3 ± 1	1.2 ± 0.2	123 ± 15	5.9 ± 0.9	1.2 ± 0.2
A ₂	225 ± 33	10.7 ± 1.9	3.3 ± 0.3	137 ± 17	4.3 ± 0.6	2.3 ± 0.2	123 ± 15	3.8 ± 0.5	2.2 ± 0.2
B ₁	132 ± 32	9.2 ± 1.7	1.1 ± 0.4	132 ± 35	8.9 ± 1.8	1.1 ± 0.5	132 ± 36	8.9 ± 1.8	1.1 ± 0.5
B ₂	169 ± 38	9.1 ± 1.6	2.2 ± 0.6	128 ± 35	5.5 ± 1.2	1.9 ± 0.6	125 ± 34	5.3 ± 1.2	1.9 ± 0.6
C ₁	128 ± 30	8.9 ± 1.7	1.1 ± 0.4	142 ± 37	9.7 ± 1.9	1.2 ± 0.5	144 ± 39	9.7 ± 1.9	1.2 ± 0.5
C ₂	170 ± 38	8.8 ± 1.6	2.3 ± 0.6	138 ± 36	5.9 ± 1.4	2.1 ± 0.6	135 ± 36	5.8 ± 1.3	2.1 ± 0.6

Data presented as means ± SD. AUC values are for 48-hour intervals.

Gentamicin exposure was simulated after six dosing regimens. Figure 2 shows the simulated plasma concentration-time profiles (mean of 1,000 simulations) for both every other day and daily regimens. Postdialysis dosing regimens (A₁ and A₂) led to about 90% of simulated subjects achieving C_{max} ≥ 8 mg/l after the first dose but almost none of the subjects achieving this target after the second and third doses. With predialysis dosing, about 70–80% of simulated subjects achieved a C_{max} ≥ 8 mg/l after all doses of the every other day regimens (B₁ and C₁) and after the first dose of the daily dosing regimens (B₂ and C₂; tables 3, 4).

The calculated 48-hour AUC values based on simulations showed that, although all subjects achieved AUC

≥ 140 mg·h/l/48 after the first dose in regimens ‘A₁’ and ‘A₂’, only 33–44 and 12% achieved it after the second and third doses, respectively. Predialysis every-other-day regimens resulted in 37–50% of simulated subjects achieving an AUC ≥ 140 mg·h/l/48 h. Similarly, less than 50% of simulated subjects achieved this target after the predialysis daily regimens (except for following first dose).

Discussion

Estimated gentamicin systemic clearance was 7.6 ml/min with a mean calculated elimination half-life of approximately 35 h. This estimate of half-life during inter-

Table 4. Percent of simulated subjects achieving AUC and peak and trough concentration targets following each of the six simulated dosing regimens

Regimen	Day 1					Day 3					Day 5				
	AUC, mg·h/l			C_{max}	C_{min}	AUC, mg·h/l			C_{max}	C_{min}	AUC, mg·h/l			C_{max}	C_{min}
	≤240	≥140	140–240	≥8 mg/l	<2 mg/l	≤240	≥140	140–240	≥8 mg/l	<2 mg/l	≤240	≥140	140–240	≥8 mg/l	<2 mg/l
A ₁	86.9	98.6	85.5	87.1	58.5	100	32.7	32.7	0.2	99.5	100	11.8	11.8	0	99.9
A ₂	42.3	99.7	42	89.4	0	100	43.5	43.5	0	9.3	100	11.2	11.2	0	18.9
B ₁	100	37.2	37.2	77.8	97.2	99.9	37.2	37.1	70.8	93.9	99.8	37.7	37.5	70.9	93.5
B ₂	96.4	76.5	72.9	77.9	39.1	99.7	32.1	31.8	2.1	57.8	99.8	29.1	28.9	1.3	60.5
C ₁	100	32.2	32.2	72.7	98	99.3	48.6	47.9	81.5	91.5	99.1	50.1	49.2	82.3	89.8
C ₂	96.1	75.9	72	71.8	32.8	99.1	44.1	43.2	6.9	46.5	99.5	41.7	41.2	5.2	47.5

Data presented as percent of 1,000 simulated subjects achieving AUC between 140 and 240 mg·h/l/48 h, below 240 mg·h/l/48 h, or above 140 mg·h/l/48 h, and percent of 1,000 simulated subjects achieving $C_{max} \geq 8$ mg/l and $C_{min} < 2$ mg/l. AUC on day 5 excludes the last 24 h of the week period.

dialysis periods is similar to what was estimated previously [8]. Similar estimates of gentamicin systemic clearance during interdialytic periods have also been reported [11, 12]. Dialytic clearance was estimated to be 134 ml/min in our study. Previous studies have reported dialysis clearance values between 78 and 116 ml/min [8, 11–14].

Results of the simulations showed that with postdialysis dosing, although 80–90% of subjects may achieve a $C_{max} \geq 8$ mg/l following the first dose, none of the simulated subjects achieved that target after subsequent doses. On the other hand, predialysis dosing regimens performed similarly and better than postdialysis regimens in terms of percent of simulated subjects achieving $C_{max} \geq 8$ mg/l. More than 70% of simulated subjects achieved a $C_{max} \geq 8$ mg/l after all doses of every-other-day dosing regimens (B₁ and C₁). These results indicate that predialysis dosing of gentamicin may perform better than postdialysis regimens in achieving effective concentrations due to the presence of remaining gentamicin concentrations from the previous dose. The above results also show that every-other-day predialysis dosing performs better than daily dosing in terms of achieving efficacy targets. This might be due to the smaller dose used with daily regimens and the inability to increase such dose due to the associated risk of toxicity.

In terms of the toxicity target, every-other-day regimens performed generally better than daily regimens. Less than 20% of the subjects achieved a $C_{min} < 2$ mg/l after the daily dosing regimen (A₂) and only 33–61% achieved the same target after the daily regimens (B₂ and

C₂). These results indicate that daily dosing in patients on SDHD may lead to sustained high trough concentrations potentially predisposing to aminoglycoside toxicity. Hence, every-other-day dosing is more suitable to allow for adequate removal of gentamicin between doses. The above results also show that predialysis and postdialysis dosing may perform the same when it comes to achieving nontoxic concentrations. This is expected given the fact that dosing before or after the dialysis would have a greater effect on the peak rather than trough concentrations.

Achievement of predetermined exposure targets was also assessed using 48 h interval AUC values. All six dosing regimens performed similarly in terms of achieving a toxicity target of AUC ≤ 240 mg·h/l/48 h with all subjects achieving this target (except for first dose of regimen A₂). Unlike the results of the peak concentrations, the predialysis regimens performed worse than the postdialysis regimens in terms of achieving an AUC ≥ 140 mg·h/l/48 h after the first dose. After subsequent doses, regimen 'C' performed consistently better than regimen 'B' with almost 50% of the subjects achieving the AUC target in regimens 'C₁' and 'C₂' after all subsequent doses assessed. Although worse after the first dose, regimen 'C' still performed better than regimen 'A' after subsequent doses. Taking these results together with the results of peak concentrations, we can conclude that predialysis dosing performs generally better than postdialysis dosing in terms of achieving effective gentamicin concentrations.

The results were compared to those obtained previously from simulations of every-other-day dosing in sub-

jects undergoing thrice-weekly hemodialysis [8]. Percentages of simulated subjects achieving $C_{\max} \geq 8$ mg/l were similar between the two studies for all doses. On the other hand, all three regimens performed better in our study in terms of achieving the toxicity target of $C_{\min} < 2$ mg/l. This can be due to differences in the effectiveness of the dialyzer used in our study or due to the more effective removal of gentamicin with more frequent dialysis sessions. Such results indicate that regimens B_1 and C_1 may be as effective and less toxic when given to subjects undergoing SDHD compared to subjects on thrice-weekly hemodialysis. The more frequent dialysis with SDHD is expected to enhance gentamicin removal leading to lower trough concentrations while achieving peak concentrations similar to those achieved with thrice-weekly hemodialysis.

This study has some limitations. Data used to develop the pharmacokinetic model were obtained from a relatively small sample of dialysis patients. Also, our data did not include pharmacodynamics measurements of drug efficacy or institutional minimum inhibitory concentration values. This study, hence, represents a pharmacodynamics simulation study that predicts drug efficacy based on simulated exposure. This is a relatively common approach that has been used before to help guide dosing regimens in special patient populations.

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Conclusions

Gentamicin is effectively removed during SDHD using the Exeltra 150 dialyzer with an estimated Cl_{dial} higher than reported in previous studies. Results of the simulations indicate that predialysis every-other-day regimens may be as effective and less toxic than postdialysis regimens and that the same every-other-day regimens can be used for subjects undergoing thrice-weekly or SDHD.

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Disclosure Statement

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